Studies on the Evolution of PMTA and TPD

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Abstract: The Premarket Tobacco Application (PMTA) and Tobacco Products Directive (TPD) are two regulatory frameworks for the contemporary U.S. and EU tobacco regulations respectively. In this study, the development and evolution of PMTA and TPD are studied, as well as regulatory rules and related practice cases. Based on the origin, evolution and access system of tobacco products as the main logical framework, from which we can see the trend of next generation products (NGPs) regulation. The PMTA's attitude does not negate flavored tobacco products, but requires scientific research based on facts. TPD is working to continuously improve and revise the underlying rules and expand their application across the EU. In the U.S., very few tobacco companies have been able to meet the FDA's strict PMTA requirements, although some companies that have not received market granted order (MGO) continue to sell products in the market, most tobacco companies, especially e-cigarette companies, have been forced to withdraw from the market. The EU is constantly tightening and refining the regulatory interpretation of TPD, so as to constrain tobacco companies with stronger regulations. Although PMTA and TPD are not consistent in terms of regulations, the evolution of the two regulations is consistent, and both are committed to gradually reducing the appeal of tobacco products to youth and non-smokers, highlighting the importance of tobacco harm reduction.

Keywords: PMTA; TPD; Tobacco Products; Regulation

1. PMTA

1.1 PMTA's Origin

PMTA, a pre-market tobacco application launched by the U.S. Food and Drug Administration (FDA), which means that tobacco products that are marketed in the U.S. need to be reviewed by the FDA after February 15, 2007. The tobacco products needs to consider whether the product is good for public health. In July 2017, the FDA announced the PMTA, and requires all electronic cigarette (e-cigarette) brands and manufacturers must submit PMTA application before August 2022, all new tobacco products must be obtained before marketing application authorization to sell in the us market, any PMTA program, namely tobacco before marketing review approval products, cannot be legally sold in the United States. Under ederal regulations, products that have not undergone PMTA procedures will be considered counterfeit or illegal, in order to better standardize the industry.

1.2 The Main Evolution Process of the PMTA

When e-cigarettes appeared on the market of U.S. in 2006, there were no specific regulatory measures to regulate e-cigarettes. On June 22, 2009, the Family Smoking Prevention and Tobacco Control Act (TCA) was signed into law, giving PMTA a basis for existence. The act gives the FDA the authority to regulate how tobacco products are manufactured, distributed and sold. Although the law initially applied to combustible cigarettes and smoke-free tobacco products, the law also gave the FDA the authority to decide which tobacco products were covered by the law. Tobacco products that are required to submit a PMTA are defined by the TCA as *new tobacco product*, which refers to any tobacco product that was commercially sold in the U.S. after February 15, 2007 other than the tobacco product under test, or after February 15, 2007, tobacco products with changes in packaging design, nicotine content, form of nicotine

transmission, smoke composition, additives, etc. As a result, the FDA issued the "Deeming Rule" in May 2016, expanding its regulatory scope to include electronic nicotine delivery systems (ENDS), also known as e-cigarettes. As a result, in February 2020, the FDA began to fully regulate flavored e-cigarettes, requiring those manufacturing and selling e-cigarettes to submit PMTA applications by September 2020, or continue to sell on the market will be considered illegal. If a PMTA has been submitted, the product is allowed to remain on the market for up to one year, during which time the FDA can enforce the law based on the results of the PMTA review, and even if it is still under review, the product will be deemed illegal by September 2021 at the latest, which is why the vast majority of companies on the FDA's list of MDOs (Marketing Denial Orders), received MDOs in September 2021.

1.3 U.S. FDA's Comprehensive Regulatory System

Before the NGPs were introduced to the U.S. market, companies must submit and grant their marketing applications to the FDA. There are currently three ways for new tobacco products to enter the market in the U.S.: PMTA, SE (Substantial Equivalence Report), and EX REQ (Exemption Request). SE is applicable to the marketing of traditional combustible cigarettes, cigars, smokeless tobacco products (traditional oral tobacco, chewing tobacco and snuff), hookahs, and self-rolled cigarettes, which means that, in relation to the tobacco product applied for, it has the same characteristics as a tobacco product already placed on the market, or have different characteristics, but clinical studies have shown that the product does not pose a public health concern. While the EX REQ is applicable to the increase or reduction of the type and quantity of additives in tobacco products currently on the market (Table 1).

Table 1. Major New Tobacco Access Policies in the U.S.

	PMTA	SE	EX REQ
Regulatory principles	The PMTA must certify that the new tobacco products are "suitable for the protection of public health", and need to consider the likelihood that existing tobacco product users will quit smoking.	The SE should demonstrate that a new product has the same or different characteristics as an existing product, but does not cause a different public health problem.	Waivers to prove substantial equivalence may be considered for modifying a tobacco product by adding or removing additives, or by increasing or decreasing the number of existing additives.
Main scope of application	All tobacco products	Mainly applicable for cigarettes, cigars, hookah, smokeless tobacco, etc.	Mainly applicable for cigarettes, cigars, hookah, smokeless tobacco, etc.

In February 2020, the FDA has issued a policy regulating the flavored e-cigarettes. The policy specifies that flavored ENDS will be restricted except for tobacco or menthol flavored e-cigarette products, and any flavored ENDS including tobacco and menthol flavors will no longer be sold to minors (Table 2).

More clarity can be found in the FDA's Technical Project Lead Review of PMTAs published on September 17, 2021. The FDA believes, based on its consideration of existing research, that e-cigarettes, particularly flavored e-cigarettes, pose a significant risk, especially to youth who do not use e-cigarettes [1]. E-cigarette use among U.S. teens surged in 2018, peaking in 2019 (27.5% of high school students and 10.5% of middle school students), with flavored e-cigarettes being a key driver. After the enforcement of flavored e-cigarettes in 2020, there was a decrease in youth e-cigarette use (19.6% of high school students and 4.7% of middle school students).

In 2020, the U.S. Centers for Disease Control and Prevention (CDC) conducted a survey on e-cigarette use among middle and high school students in the United States. Research shows that adolescent e-cigarette users are more likely to use flavored e-cigarettes than adult e-cigarette users. In 2020, 82.9% of middle school students use flavored e-cigarettes, 76% of open tank system e-cigarette and 87% of closed tank system e-cigarette users prefer to use flavored products. Among them, fruit flavor is the most popular, 81.7% of open tank system e-cigarette were fruit flavored, 82.7% and 66% of disposable e-cigarettes and

cartridge e-cigarettes were fruit flavored. A study examined the relationship between the initiation and subsequent use of flavored tobacco products among adolescent and adult tobacco product users from 2013 to 2015 in the U.S. showed that e-cigarette users of different ages largely had their first e-cigarette flavored (12-17 years old accounted for 80%, 18-24 years old accounted for 75%, and over 25 years old accounted for 58%)[2].

Table 2. Other Major E-Cigarette Regulatory-Related Policies in the U.S.

Policy Progress	Time	Primary Coverage
Tobacco determination rules	May, 2016	All products that meet the statutory definition of tobacco products (including cigar, pipe, water pipe and electronic nicotine delivery system products) are included in their regulatory authorities.
Flavor ban	February, 2020	FDA: Flavored e-cigarettes (except tobacco or menthol flavored e-cigarette products) were banned. Selling any tobacco product to minors is prohibited.
	September 2019	State: Imposing a temporary fragrance injunction, some of which are prohibited by the court but partly permanent.
The Prevention of All Cigarette Trafficking Act extends to ENDS and non-ENDS products	October, 2021	Mailing e-cigarettes to consumers is prohibited, but merchants are allowed to mail each other with a license.
Federal legislation applies the TCA to any ENDS product containing nicotine	March, 2022	ENDS products containing any nicotine are applicable to the requirements of FDA pre-market tobacco applications.

Because adolescence is a critical period of a person's neurological and psychological development, the adolescent brain is more susceptible to the effects of nicotine than the adult brain[3]. Research has shown that early exposure to nicotine in adolescence can enhance the rewarding or reinforcing effects of nicotine in adulthood and may cause long-term or short-term deficits in attention and memory[4].When focus on the prevalence of flavored e-cigarette and cigar use among adolescents and adults in 2016-2017, 83.7% of young adults' first e-cigarette use was a flavored e-cigarette [5]. the FDA investigated the continued use of flavored e-cigarettes by adolescents in Connecticut in 2014 and adolescents in California 2014-2017 after using flavored e-cigarettes for the first time. It is believed that flavored e-cigarettes will not only lead to smoking flavored e-cigarettes easier to get started, due to their frequent and repeated use, leading to the establishment of a habit of regular use, and eventually forming a dependence on nicotine[6, 7].

1.4 PMTA Review Process

The application process for PMTA is cumbersome and is divided into five phases (Figure 1).

Figure 1. PMTA Review Process

In PHASE 0, the applicant submits to the FDA for an application meeting, where the Center for Tobacco Products (CTP) staff will discuss with the applicant their plans for submitting the PMTA. Applicants will receive either a meeting granted letter or a meeting minutes letter, or a meeting denial letter. In PHASE 1, FDA will further inspect the products applying for PMTA to ensure that the products fall under the jurisdiction of CTP and confirm that the application meets the statutory and regulatory requirements of Section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the criteria set forth in § 1114.27(a)(1). In this phase, about 19.494 million products were rejected, of which the FDA's review was particularly high between October 2022 and the end of February 2023, rejecting 17.277 million product applications. In PHASE 2, After being *accepted* for further review, this phase mainly checks whether important data or information of the applied products is missing. The FDA defines *accepted* as having met the minimum criteria for approval, allowing for further review. As

of February 28, 2023, FDA has passed the information integrity review of 1.088 million products and rejected about 5.111 million products that are missing relevant key information. In PHASE 3, FDA will conduct scientific tests on the applied products in microbiology, pharmacy, toxicology, clinical medicine, epidemiology, sociology and other aspects. If all the tests pass, it is proved that PMTA has been passed, and the Marketing Granted Order (MGO) is granted. Otherwise, a Marketing Denial Order (MDO) will be issued. So far, a total of 23 e-cigarettes, 2 combustible cigarettes, 8 NGPs including devices, and 4 other new tobacco products have passed PMTA after 2019; At least 1.23 million e-cigarette products have received MDOs, and the number is growing.

2. PMTA Applications Cases

After 2021, the PMTA review will be accelerated, and the approval results of major brand products will be released successively. At present, the NGPs that have passed the PMTA are all tobacco flavors.

2.1 iQOS

On March 31, 2017, Philip Morris International (PMI) submitted a PMTA application for iQOS to the U.S. FDA Tobacco Products Center. In August of the same year, the FDA has completed the preliminary review of the iQOS PMTA and has accepted the application for substantive review of the iQOS. On April 30,2019, the FDA officially issued a statement that Philip Morris U.S., its heated non-burning e-cigarette product iQOS was approved by the FDA PMTA, which means that iQOS can be sold in the U.S. as a tobacco product label, and the U.S. market of heated non-burning e-cigarette opens. The FDA's approval of iQOS for sale is based on the product's potential to stop or reduce smoking in current smokers, its ability to protect public health due to the reduction of harmful components in its emissions, and the likelihood that people who do not use tobacco products will not or rarely start using tobacco products. Ultimately, after FDA review, the iQOS device and the three Marlboro heatstick brands can be sold in the U.S. market. PMI has submitted its latest product, iOQS ILUMA, to the FDA, as well as its PMTA for TEREA, a heatstick.

2.2 Reynolds Vuse

In October 2019, Renolds Tobacco (RJ Reynolds, RJR), a subsidiary of British American Tobacco (BAT), submitted a PMTA for Vuse Solo and multiple flavor supplement cartridges to the FDA. On November 22 of the same year, FDA issued the document acceptance. Subsequently, FDA reviewed Vuse Solo twice, the first round was completed on May 19,2020, then a defect letter was sent, RJR supplemented and responded; the second round of FDA review was completed on October 12, 2021, and MGO license was issued. On October 13,2021, the US FDA allowed BAT's RJR to sell three of its Vuse e-cigarette products. These three products are: Vuse Solo Power Unit, Vuse Replacement Cartridge Original 4.8% G1 and Vuse Replacement Cartridge Original 4.8% G2. Although the above three products passed the PMTA, RJR received FDA MDOs for its other fruit-flavored e-cigarettes, but the mint flavor was not affected.

3. TPD

3.1 TPD's Origin

TPD (Tobacco Products Directive), the European Union Tobacco Directive (2014 / 40 / EU), which is used to regulate and supervise the manufacture, sale, display (product design, packaging, etc.) and all tobacco and tobacco-related products (such as e-cigarette products). The TPD is an EU directive administered to EU member states, which requires them to convert it into their domestic laws and enforce it by 20th May 2016. When converting the EU directive into the domestic laws of the EU member states, the laws of different countries vary slightly, so there are different requirements. Before the products are exported to the EU, the products should understand the legal requirements of the destination country in detail to avoid non-compliance.

On 26th February, 2014, the European Parliament formally approved the revised TPD and related products DIRECTIVE (2014 / 40 / EU), replacing the old version of the Directive 2001 / 37 / EC, accustomed to call 2001 / 37 / EC as TPDI and 2014 / 40 / EU as TPD II. The 2014 / 40 / EU came into effect on 20 May 2016, and for the first time included

e-cigarettes under the control of the Tobacco Products Directive.

3.2 The Main Evolution Process of the TPD

On 5 June 2001, the European Parliament and the Council issued Directive 2001/37 / EC to regulate and harmonise the production and marketing of tobacco products in the member states of the EU. Subsequently, on September 5, 2003, the relevant contents of packaging were further stipulated. In the days that followed, TPD was continuously optimized and improved to expand its scope and adapt to the ever-evolving and changing tobacco market (Table 3).

Table 3. 2001-2022 Main Regulatory Evolution of TPD

Time	Directive	Content
5.Jun.2001	Directive 2001 / 37 / EC	The Directive provides for the approximation of laws, regulations and administrative provisions concerning the manufacture and sale of tobacco products in the member states.
5.Sep.2003	Commission Decision No.2003 / 641 / EC	The decision focus on the use of color photographs or other illustrations as health warnings on tobacco packaging.
7.Mar.2012	Directive 2012 / 9 / EU	The directive amended Annex I of the European Parliament and Council Directive 2001 / 37 / EC, to the approximation of the laws, regulations and administrative provisions of the member states on the manufacture, display and sale of tobacco products.
26.Feb.2014	Directive 2014 / 40 / EU	This Directive adopts the Law of the European Parliament and of the Council of member states on the display and sale of the manufacture of tobacco and related products and repeals Directive 2001/37 / EC.
10.Oct.2014	Directive 2014 / 109 / EU	the Commission authorized Directive 2014 / 109 / EU to amend Annex II of the European Parliament and Council Directive 2014 / 40 / EU to establish a picture warning gallery for tobacco products.
18.May.2016	Decision 2016 / 787 (EU)	The decision provides for a priority list of additives contained in cigarettes and self-rolled tobacco, subject to stricter reporting obligations.
15.Dec.2017	2018 / 574	The Commission Implementing Regulation (EU) provides for the establishment and operation of technical standards on traceability systems for tobacco products
2021	Annex II to the European Economic Area Agreement	The purpose of the Act is to include the Tobacco Products Directive 1, including Directive 2 authorized by its Amendment Committee, in the EEA Agreement and in accordance with the EEA Agreement Directive 2001 / 37 / EC 3.
29.Jun.2022	Directive (EU) 2022/2100	The Directive supplemented and amended the unclear regulation of heated tobacco products in the TPD and expanded the scope of application of the provisions to heated tobacco products.

3.3 Major Changes from TPD 1 to TPD 2

3.3.1 Composition and emission standards for tobacco products

TPD 2 refers to the 2014 amendment and replacement of the 2001/37/EC formed in 2001 and the new 2014/40/EU, which aims to reduce the differences in the regulation of tobacco products between EU member states and supplement the regulation of certain tobacco products (such as e-cigarettes). In terms of measuring the composition and emissions of tobacco products, tar of cigarettes should be measured in accordance with ISO standard 4387, nicotine should be measured in accordance with ISO standard 10315, and carbon monoxide should be measured in accordance with ISO standard 8454. In addition, EU member states should require manufacturers or importers of tobacco products to submit to the relevant national authorities lists of all ingredients used in the manufacture of tobacco products and their content, emission levels for each emission, consumer preference studies and market studies.

With regard to additives, member states should not ban the use of additives that are essential

for the production of tobacco products. For example, sugar can replace sugar lost during baking, as long as these additives do not produce characteristic flavors and do not significantly or measurably increase the addictive, toxic, or CMR properties of tobacco products. However, it is not required to add additives that can make tobacco products be beneficial to health or reduce health risks, nor can it add substances related to energy or vitality (such as caffeine, taurine, etc.), and TPD is even refined to prohibit the use of substances that will color the smoke emitted from smoking, while also prohibiting additives that can cause flavor characteristics.

3.3.2 Packaging and warnings

The revision of the packaging requirements of tobacco products is a more prominent part of the TPD 2 amendment, and the outer packaging of tobacco products should bear a warning in the member state's official language, and the warning cannot be obscured or hidden for any reason. TPD 2 specifies the font, size and area of at least 65% of the front and back of the warning, and also specifies the size of the cigarette pack. For those tobacco products that do not include cigarettes, hookahs, roll-your-own cigarettes (RYO), HTPs but include e-cigarettes, the warnings shall cover at least 30% and 40% of the surface area of the outer package, at least 32% and 45% in the case of a member state with two official languages and, in the case of a member state with three or more official languages, should account for more than 35% and 50%. In addition, the EU published three sets of pictures, a total of 42, requiring all member states to print on each tobacco product randomly and evenly, and set the size of the picture.

The pictures and health warnings on the packaging of tobacco products under the regulation of TPD 2 are more prominent than the plain text warnings under the regulation of TPD 1, but the cognitive and behavioral responses of consumers have not decreased, and there is no significant increase [8]. Previous research has shown that the effectiveness of warning labels declines over time [9]. A study published in *THE LANCET* in 2021 showed that although iQOS usage is currently low in the EU (in 2021, the survey study indicated that 6.5% of survey participants in the EU had used HTPs, 1.3% were current users, and 0.7% were daily users), The Czech Republic, Cyprus and Italy have the highest proportion of HTPs users in the EU, with almost a third of HTPs users quitting or cutting down on smoking [10]. However, in areas such as the EU, where external packaging regulations are strict, HTPs do not fully implement the packaging regulations in accordance with TPD, only printed warnings, no warning pictures. This shows that the harm reduction properties of HTPs have been acquiesced in the EU, although the EU has not expressed this attitude directly.

3.3.3 Advertising

The EU believes that tobacco advertising increases the consumption of tobacco products in several ways, most importantly having the potential to encourage children or youth to start smoking, while also reducing smokers' motivation to quit, urging former smokers to resume smoking and creating an environment where tobacco use is acceptable. Advertising, sponsorship and promotion of tobacco product have the potential to promote the consumption of tobacco products, enforcement of bans on advertising, sponsorship and marketing of tobacco products should therefore be strengthened [11]. Therefore, the EU has formulated a series of legal provisions based on the Framework Convention on Tobacco Control (FCTC) to restrict tobacco advertising. In the Tobacco Advertising Directive (2003/33/EC), the EU set out the following provisions. The directive prohibits tobacco advertising in newspapers and other print publications, except those specifically aimed at people in the tobacco trade and those published in countries outside the EU. The directive prohibits all forms of radio advertising of tobacco products, while tobacco companies cannot sponsor radio programs or large-scale events with cross-border impact, nor can they distribute tobacco products for free. Product placement advertisements for tobacco products are prohibited in films, television dramas and other media.

4. Summary of the TPD

In general, the EU TPD mainly focuses on production access, making detailed descriptions of the composition of tobacco products, on this basis, the member states are required to implement the directive, and the implementation of the measures to the

European Commission (EC). But the pace of evolution of NGPs is very fast, even the regulation of additives needs to be constantly adjusted. Just as HTPs were incorporated into TPD before the market expanded, the changing product landscape may have created problems with the relevance of TPD to innovative and new products, and changes in these products may well have been expected.

TPD not only controls the access of tobacco products from the aspect of additives, but also provides for traceability. The EU Unique Device Identifier requires member states to ensure that all tobacco product unit packaging is marked with a unique identifier that, like the warning, cannot be hidden or erased, reflecting the traceability of the product. The severity of the EU tobacco products access system depends on the standards of the member states for the sale of tobacco products, TPD and CEG (EU Common Entry Gate) are only the threshold for tobacco products to enter the EU market, and each member state can raise the threshold at this minimum standard, or it can only require tobacco companies to report to the authorities. Specially, CEG is an information technology tool designed to ensure uniform reporting of information on tobacco products, e-cigarettes and refill containers. In terms of the minimum purchase age of tobacco products, TPD does not make provisions, and each member state sets its own, such as Belgium and Austria, the minimum smoking age is 16 years old, which also leads to the serious problem of youth smoking. Label packaging and advertising reflect the government's concern in smoking control, on the contrary, the EU in the label, packaging, advertising supervision is particularly strict, strict packaging and advertising regulations can reduce more people smoking to a certain extent, but cannot greatly affect the people who are smoking, such as in countries or regions printed with warning pictures of people using private cigarette box habit. Warning pictures are not a reason for smokers to stop smoking.

5. Conclusion

In general, the FDA requires all NGPs to undergo an exhaustive PMTA review prior to marketing to ensure that the benefits of the product outweigh the potential risks. However, this study found that so far, only a small number of tobacco companies can meet the FDA's strict PMTA requirements to obtain MGO, and most companies, especially e-cigarette companies, are more likely to receive MDO in the current FDA enforcement and are forced to withdraw from the market. Larger companies have more resources to meet the onerous PMTA application requirements. In contrast, the vast majority of the 275 companies that received MDOs were independent e-cigarette manufacturers that primarily featured flavors. Most of these manufacturers cannot afford the high cost of experimental testing, and it is more difficult to meet the FDA's stringent safety and harm reduction standards on their products. From this perspective, the market concentration of the tobacco industry will be further strengthened in the future.

The FDA originally focused on traditional combustible cigarettes, but as e-cigarettes became more popular, the FDA changed its attitude and began to closely regulate e-cigarettes and other NGPs, which shows that the FDA is paying increasing attention to the public health impact of NGPs, especially on adolescents. The enterprises that obtain MGO are mainly subsidiaries of large traditional tobacco companies. Although the product categories through PMTA are involved, the taste review is stricter, e-cigarettes are only limited to original taste. While the FDA has a strong taste control, it does not directly deny the existence of flavored tobacco products, the FDA is seeking a balance between the risks to youth and the benefits of adult smoking groups. The EU TPD is also constantly being refined and revised to face the evolving tobacco products. On November 23, 2022, the EU adopted a measure banning the sale of flavored heatstick of HTP in the EU, and the flavor ban was implemented on July 23, 2023, came into force on October 23, 2023. The TPD already rigorously regulates the packaging, labeling and advertising of tobacco products, and as seen in recent moves in the EU, the TPD is now further tightening restrictions on flavored tobacco products. This is different from the U.S. PMTA, which requires more evidence-based scientific research to prove that flavored products do not affect teenagers, while TPD is more direct.

In conclusion, the next steps for the FDA and the EU can be expected to maintain strict

regulation of the e-cigarette and tobacco product markets, while making modest openings in certain areas or products based on changes in research data (if the research results support it). Although PMTA and TPD are not in accordance with each other on the regulation articles, yet the evolution of both regulations is the same, which is to highlight the importance of tobacco harm reduction, and reduce the attraction of youth consumption. In the future, both regulations will be stricter. The FDA is likely to improve the regulatory system while providing a living space for products that have been proven to have a certain effect, but the EU will further tighten restrictions. Overall, the FDA's rigorous and enlightened policy direction is expected to achieve regulatory goals without unduly restricting market innovation and consumer choice.

Acknowledgements

This work was supported by Yunnan Tobacco Science (2021) 51:2021530000241010.

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